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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/776,466 | 02/02/2001 | Burton G. Christensen | P-087-R | 7142 |

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| EXAMINER | |
|---|---|
| LUKTON, DAVID | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | 8 |

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/776,466 | Applicant(s) CHRISTENSEN ET AL. | |
|---|---|---|---|
| | Examiner David Lukton | Art Unit 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 8 (filed 6/27/03), claims 17, 18, 20 have been amended, and claims 19 and 21 cancelled. Claims 1-18, 20 are pending.

Applicants' arguments filed 6/27/03 have been considered and found persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is asserted in the specification (page 109, line 17+) that that the claimed compounds were "active" in certain in vivo tests. The only *in vivo* tests which are described are the "mouse septiciemia model" (page 108, line 15+), and the mouse "neutropenic thigh model" (page 108, line 27+). However, no data are presented, and it is not clear what the criteria are for a compound to be considered "active". The "neutropenic thigh model" is described only briefly in the specification (page 108, line 27+). Additional examples of the "neutropenic thigh model" can be found in each of the following references: Boylan Carole J (*Antimicrobial Agents and Chemotherapy* **47** (5) 1700-6, 2003); Rocchetta H L

(*Antimicrobial Agents and Chemotherapy* **45** (1) 129-37, 2001); Mouton J. W., (*Antimicrobial Agents and Chemotherapy* **43** (10) 2473-8, 1999). As is evident, some analysis of the data is required. It may be the case the skilled microbiologist would be able to determine an "$ED_{50}$" parameter. But the question is, what are the minimal criteria for a compound to be "active"....? It is apparent that some statistical analysis would be required, particularly for the case in which a quantity of (alleged) antibacterial agent selected is sufficiently low as to be just above the threshold to produce a result that is "statistically significant". As applicants may be aware, it is not uncommon for artifacts in statistical analysis to occur. This matter is discussed in each of the following references:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* **28** (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (*Chronobiology International* 18 (6) 1041-53, 2001).

Consider next the "mouse septiciemia model". Suppose that 10 mice are inoculated with

*S. aureus,* and that these 10 mice are divided into two groups of 5 mice each, i.e., "group 1" and "group 2". Suppose that one of the claimed compounds is administered to the 5 mice in group 1, and that "vehicle" only is administered to the 5 mice in group 2. Suppose that the result of this is that 3 of mice in group 2 mice died, and 2 lived, and that 3 of the mice in group 1 lived and 2 died. In applicants' opinion, would this constitute evidence of "activity"....? To a statistician, such a result would not be meaningful.

What is suggested is that applicants provided specific, quantitative data which shows the activity of the claimed compounds either *in vitro* or *in vivo*. In the event that only *in vitro* data is provided, those claims that recite the term "pharmaceutical composition" will remain rejected.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, structure/activity relationships of antibacterial compounds are unpredictable. Consider, for example, the following:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and

testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.

These and other references disclose that there do exist compounds which exhibit no antibacterial activity, and many of these inactive compounds are structurally analogous to compounds that <u>are</u> active. The key point is that the factors which give rise to activity or inactivity are unknown in the art; and certainly applicants have made no attempt to discuss such factors.

With regard to the "pharmaceutical composition", this term carries with it the implied assertion of therapeutic efficacy. As it happens, *in vitro* efficacy is not necessarily predictive of *in vivo* efficacy. For example, Otvos (*Protein Science* **9** (4) 742-9, 2000)

discloses an example of a compound which is active *in vitro* but not *in vivo*. In addition, diseases caused by bacteria can be rather difficult to treat, even under the best of circumstances. Diseases caused by bacteria include the following:

> Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, Yellow Fever

Which of these, exactly, do applicants believe that they can treat? If the patient is afflicted with AIDS (in addition to a bacterial infection), are the claimed compounds effective? In addition, there is the problem of antibiotic resistance. Presumably applicants are aware of this, but if not, the following two articles discuss this matter:

> Liu (*Advances in Experimental Medicine and Biology* **455**, 387 1999)
>
> Monroe (*Current Opinion in Microbiology* **3**(5) 496-501, 2000).

Specifically with regard to endotoxin-associated conditions, consider the following: Corriveau C. C. "Antiendotoxin therapies for septic shock" (*Infectious Agents and Disease*, **2** (1) 44-52, 1993) discloses that there have been numerous attempts over the years to treat human septic shock by inhibiting, neutralizing, or clearing endotoxin, and that the results of those attempts support a conclusion of "unpredictability" in the treatment of the same.

Accordingly, (a) one cannot predict antibacterial activity merely by viewing a structure, (b) "undue experimentation" would be required to determine which of the claimed compounds will inhibit bacterial growth, and (c) even if it were true that the compounds exhibited antibacterial activity *in vitro*, "undue experimentation" would be required to determine which of the claimed compounds can be used to treat even one disease caused by bacteria, to say nothing of the considerable number of diseases that one would have to test for therapeutic efficacy against.

It remains the case that "undue experimentation" would be required to determine which, if any, of the claimed compounds can exhibit antibacterial activity (when not combined with a known antibacterial agent). It is suggested that applicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted; also suggested is that the term "pharmaceutical" be deleted from whichever claims recite it.

✹

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600